Remarks

Claims 1, 2 and 8-28 are pending in the application. Claims 1, 2 and 8-28 have been rejected. Claims 1, 9, 11, 12, 15, 17, 18, 20, 21 and 24 are amended.

Applicants submit that the amendments herein introduce no new matter. Claims 1 and 15 are amended to more clearly set forth the use of an amphiphilic wetting agent. Support for these amendments can found throughout the application and drawings as originally filed (see, e.g., paragraph 0021). Claim 17 is amended to depend from claim 15, rather than claim 1. In response to the Examiner's suggestion, claims 9, 11, 12, 18, 20 and 21 are amended to more particularly point out and distinctly claim the subject matter of the invention. Favorable reconsideration in light of the amendments and remarks which follow is respectfully requested.

The amendments herein do not constitute an admission regarding the patentability of the amended subject matter and should not be so construed. Amendments to the claims were made for purposes of more clearly stating the claimed subject matter and do not add new matter or alter the scope of claims.

Rejections under 35 U.S.C. §103

Trimmer et al. in view of Baum

The Examiner rejects claims 1-2, 8-10, 13, 15-16 and 22 under 35 U.S.C. §103(a) as being unpatentable over WO 96/10630 to Trimmer et al. ("Trimmer") in view of U.S. Patent No. 6,294,515 to Baum ("Baum"). Applicants respectfully traverse.

Regarding Applicants' previous arguments that Trimmer does not teach a method of treating the surface of microprotrusions, which a consideration of Baum does not cure, the Examiner incorporates and relies on his statements made in the Office Action mailed on January 10, 2007. In that Office Action, the Examiner stated that the term "wetting agent"

> is not defined in the specification to exclude liquids that could wet a surface. Applicants' description of wetting agents to include amphiphilic molecules is not a definition and thus does not set forth clear metes and bounds for this term (see [0021]-0022]]). Therefore, a person of ordinary skill in the art would conclude that a reasonable

> broad interpretation of the term "wetting agent" includes liquids that could "wet" a surface.

(Office Action, Jan. 10, 2007, p.4). Applicants disagree. The specification clearly describes the properties of "wetting agents" as used in the application. Referring to paragraph [0021], wetting agents are described as amphiphilic molecules, in which the hydrophobic groups of the molecules bind to a hydrophobic substrate (e.g. hydrophobic surfaces on the microprojections). Coating the hydrophobic surfaces of the microprojections with the amphiphilic agent renders the treated surfaces more hydrophilic, making them susceptible to *subsequent* wetting by a formulation. Therefore, it is not appropriate to include in Applicants' description of a "wetting agent" any liquid that can merely "wet" a surface.

Applicants submit that the use of an amphiphilic wetting agent in the manner described in the application is not disclosed or taught by Trimmer either alone or in combination with Baum. Trimmer describes the application of biological materials to the microprobes in a number of ways, including applying the solution directly onto the microprobes, stating that "surface tension alone typically will hold the biological material in place between the probes." (Trimmer, p. 11, ll. 24-35). Trimmer states that "[t]his effect can be enhanced by adding a wetting agent to the solution of biological material,..." (Trimmer, p. 12, ll. 1-2). However, the term "wetting agent" in this context refers to the process of making the biological material solution more *aqueous*. Trimmer discloses that upon exposure of the silicon surfaces of the microprobes to air, "an oxide is formed which is **hydrophilic** in nature and thus causes any aqueous biological material solution to more strongly adhere thereto." (Trimmer, p. 12, ll. 4-10) (emphasis added). Thus, rendering the solution of biological material more aqueous enhances its adherence to the *hydrophilic* surfaces of the microprobes of Trimmer.

In contrast, the microprojections of Applicants' invention have surfaces that are *hydrophobic*, such as when they are made of a metal like stainless steel or titanium. (see, e.g., Specification para. 0018). Treatment with an amphiphilic agent allows the *hydrophobic* groups of the amphiphilic molecules to bind to the relatively *hydrophobic* microprojection surfaces, making the hydrophilic groups of the amphiphilic molecules available to bind the hydrophilic solutions of pharmacologically active agents. Thus the term "wetting agent" as used by Trimmer (to increase the aqueous content of

a biological material) differs from the term as it is described in Applicants' specification, and in amended claim 1 and claim 15 of the instant application. Furthermore, Trimmer teaches away from Applicants' invention; applying an amphiphilic wetting agent to the hydrophilic silicon surfaces of Trimmer's microprobes would be counterproductive, arguably rendering the surfaces *less* hydrophlic.

The examiner also states that "it would have been apparent to the ordinary skilled artisan that exposure of the fabricated microprojections to any of the methods taught by Trimmer, albeit for shorter periods of time than those required in fabrication, would remove extraneous impurities and yield a 'clean' surface ideally suited for coating." (Office Action, Jan. 10, 2007, p. 5). The Examiner cites no authority for this supposition. Moreover, an amphiphilic wetting agent is described in Applicants' specification as altering the hydrophobic properties of the surfaces of the microprojections, and not for the purposes of cleaning their surfaces.

Trimmer describes procedures for fabricating intracellular microprobes. Some of these fabrication steps include pre-cleaning the silicon wafers with "RCA" prior to heating and growing a protective silicon dioxide layer onto the wafer (Trimmer, p. 5, ll. 26-30), using hydrofluoric acid to remove the oxide layer present on the wafer (Trimmer, p. 6, ll. 19-22), using KOH to etch the wafer until the SiO2/SiN protective regions start to float off the wafer (Trimmer, p. 6, ll. 37-38, p.7, ll. 1-4), soaking in 95% ethanol, and washing with distilled deionized water (Trimmer, p. 16, ll. 30-36). None of these steps is described as a treatment to alter the hydrophobic properties of the surfaces of microprojections.

The Examiner also states in the current Office Action that

> [i]t would have been prima facie obvious to an ordinary skilled artisan at the time of the instant invention that soap, such as the rinse agents taught by Baum, can be used to treat a surface. An ordinary skilled artisan would have had a reasonable expectation of success in cleaning a surface prior to coating using "soap/detergent", because this is a well-know use of "soap/detergent."

Applicants respectfully traverse. Baum discloses "organic materials in the form of a rinse agent concentrate that can be added to an aqueous diluent to form an aqueous rinse composition promoting

sheeting action in a rinse cycle after an alkaline detergent cycle." (Baum, col. 1, ll. 14-18). Baum describes how rinse agents appear to work:

> [t]he surfactant in the rinse aid is absorbed on the surface at temperatures at or above its cloud point, and thereby reduces the solid-liquid interfacial energy and contact angle. This leads to the formation of a continuous sheet which drains evenly from the surface and minimizes the formation of spots.

(Baum, col. 1, ll. 49-52). Baum does not teach the use of amphiphilic wetting agents to alter the hydrophobic properties of surfaces such as those of the microprojections of Applicants' invention. The Examiner states that "Applicants have provided no data or persuasive arguments as to why an ordinary skilled artisan would not have a reasonable expectation of success of cleaning a surface with soap prior to coating said surface with a coating formulation." Applicants point out that the Specification does not describe an amphiphilic wetting agent as a cleaning agent; it is described as an agent that alters the hydrophobic properties of the surfaces of the microprojections. Thus the deficiencies of Trimmer are not cured by the teachings of Baum. Accordingly, combining the Baum reference with the Trimmer reference does not render claims 1-2, 8-10, 13, 15-16, and 22 obvious under 35 U.S.C. §103(a), and Applicants respectfully request reconsideration and withdrawal of their rejection.

Trimmer et al. in view of Haji et al.

Claims 24-28 are rejected under 35 U.S.C. §103(a) as being unpatentable over Trimmer in view of U.S. application publication no. 2001/0018272 to Haji et al. ("Haji"). The Examiner states that "[i]t would have been *prima facie* obvious to a person of ordinary skill at the time of the instant invention that plasma treating a silicon substrate, such as the substrate used by Trimmer to make microprobes, prior to coating would essentially clean the surface of any undesirable organic compounds and remove any native oxide present on the silicon surface." The Examiner further states that plasma treatment as a pre-conditioning treatment prior to the application of a coating formulation "is an art recognized step," and that "exposure of the fabricated microprojections to any of the methods taught by Trimmer or plasma treatment taught by Haji, albeit for shorter periods of time than those required in fabrication, would remove extraneous impurities and yield a 'clean'

surface ideally suited for coating." The Examiner cites no authority to support this supposition. Applicants therefore respectfully traverse.

Applicants point out that plasma treatment is described in the instant application as inducing the formation of pits on the microprojections in order to modify their surface properties. (Specification, para. 0019). Neither reference cited by the Examiner teaches or suggests the use of plasma treatment to achieve this result.

As noted above, Trimmer discloses the use of heat, hydrofluoric acid, and KOH for the *fabrication* of silicon microprobes. None of these are disclosed as treatments to alter the hydrophobic properties of the surfaces of microprojections. In addition, Trimmer discloses that "the microprobes and/or substrate can be physically pretreated, e.g., roughened or chemically pretreated, e.g., with a porous material to enhance the 'adhesion' between the biological material solution and the probes and substrate." (Trimmer, p. 12, ll. 10-14). Trimmer does not disclose the use of plasma treatment to modify the surface properties of microprojections.

The teachings of Haji do not cure the deficiencies of Trimmer. The Examiner notes that Haji teaches plasma treatment for etching the surface of a semiconductor wafer, or cleaning the surface of a printed circuit board. Haji discloses a device for "deep etching (for example 5 μm)," ... "to thin the wafer or to remove a stress layer (a layer having cracks by machine grinding) in the polished surface of the wafer." (Haji, para. [0003]). The plasma treatment thus described by Haji would not suggest or teach one skilled in the art the use of plasma treatment to alter the surface properties of microprojections to promote the homogeneous coating of a pharmacologically active agent.

Accordingly, at least for these reasons, combining the Haji reference with the Trimmer reference does not render claims 24-28 obvious under 35 U.S.C. §103(a), and Applicants respectfully request reconsideration and withdrawal of their rejection.

Trimmer et al. in view of Jain et al. and/or Patel et al.

Claims 11, 15-16, 19-21, and 23 are rejected under 35 U.S.C. §103(a) as being unpatentable over Trimmer and further in view of U.S. Patent No. 4,505,890 to Jain et al. ("Jain") and/or U.S. Patent No. 6,248,363 to Patel et al. ("Patel"). The Examiner references the Office Action of June 14,

2006 for the teachings of Trimmer and Jain. Jain was cited for teaching a coating composition comprising HPMC. Jain discloses a coating layer applied over the core of a tablet, including film-formers or binders, such as a hydrophilic polymer like hydroxypropylmethyl cellulose and a hydrophobic polymer like ethyl cellulose, etc… (Jain, col. 4, ll. 30 – 39). These act as "hydrocolloid gelling agents" (Jain, col. 4, ll. 49-64), that "swell to form a gelatinous mass which acts as a protective barrier," (Jain, col. 3, ll. 41-52) and which allows medicament to be "released by diffusion through the gel layer." (Jain, col. 3, ll. 46-53). This provides for a substantially uniform release of medicament over a period of 8 hours or more in a zero order release. (Id.). Jain fails to disclose or teach an amphiphilic wetting agent consisting of HPMC that can be used to alter the surface properties of microprojections.

According to the Examiner, "Trimmer suggests that the inclusion of wetting agents to the solution of biological material, or to the medium in which the method is carrie[d] out would enhance the wetting of the surface of his invented microprobes via the formation of a meniscus." The Examiner cites no authority to support the supposition that a wetting agent consisting of HPMC would enhance the wetting of the surface of Trimmer's microprobes via the formation of a meniscus. Rather, Jain teaches the use of HPMC as a "hydrocolloid gelling agent" that provides for a slow release of drug from the core of an ingested tablet. At least for these reasons, the teachings of Jain fail to cure the deficiencies of Trimmer. Accordingly, combining the Jain reference with the Trimmer reference does not render claims 11, 15-16, 19-21, and 23 obvious under 35 U.S.C. §103(a), and Applicants respectfully request reconsideration and withdrawal of their rejection.

The Examiner also cites Patel for teaching that "both lipophilic and hydrophilic surfactants are known to be useful for improving both the physical and chemical stability of active ingredients as well as enhancing absorption and bioavailability …." The Examiner notes that "surfactants are also known as stabilizers of active ingredients." Applicants must point out that the Specification describes surfactants for their use as amphiphilic wetting agents, which affect the hydrophobic properties of microprojections. These amphiphilic polymers can also be used to alter the viscosity of a solution, affecting the wettability of that solution. (Specification, para. 0022). Thus, combining the disclosures by Patel of known surfactants with the teachings by Jain of coating compositions for tablets fails to suggest the use of these compounds as amphiphilic wetting agents, and therefore does

not cure the deficiencies of Trimmer. Accordingly, combining the Jain and Patel references with the Trimmer reference does not render claims 11, 15-16, 19-21, and 23 obvious under 35 U.S.C. §103(a), and Applicants respectfully request reconsideration and withdrawal of their rejection.

Double Patenting – claims 17 and 18

The Examiner states that claims 17-18 are identical to claims 8-9, respectively. Applicants have amended claim 17 to depend from claim 15, rather than claim 1, obviating the Examiner's rejection on double patenting grounds. Reconsideration and withdrawal of the rejection is requested.

Double Patenting – claims 1 and 2

Claims 1 and 2 are rejected on grounds of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 6,855,372 ("the '372 patent") in view of Trimmer and Baum. The Examiner references the Office Action dated June 14, 2006, pages 11-12 for the reasons for the rejection. Applicants respectfully traverse.

Claims 1-12 of the '372 patent relate to a method for coating a liquid onto microprojections. None of the claims include a step of treating the surface of one or more microprojections of a microprojection array by rinsing with a solution containing an amphiphilic wetting agent, which includes a hydrophilic group and a hydrophobic group, wherein the hydrophobic group of the wetting agent binds to hydrophobic surfaces of the microprojections. For the reasons given above, neither Trimmer nor Baum, alone or in combination, teach this step. Specifically, neither Trimmer nor Baum teach or suggest the use of an amphiphilic wetting agent to alter the hydrophobic properties of the surfaces of microprojections.

Thus the claims as amended are not mere obvious variations of claims 1-12 of the '372 patent in view of Trimmer and Baum, because one of the required steps is not taught or suggested. Therefore, reconsideration and withdrawal of the rejection of claims 1 and 2 for obviousness-type double patenting is respectfully requested.

CONCLUSION

In view of the foregoing, applicants request reconsideration and allowance of all claims. A petition and fee for a three-month Extension of Time is submitted herewith. Therefore, Applicants believe that this response is timely filed with sufficient fees. In the event that Applicants are in error, the Office is hereby authorized to charge or credit Deposit Account No. **04-1105**, referencing Docket No. 80892(303655).

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Respectfully submitted,

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